Synthesis of novel α-functionalized phosphinic acid derivatives of thiophene and the first crystal structure of an α-hydroxyalkylphosphinate

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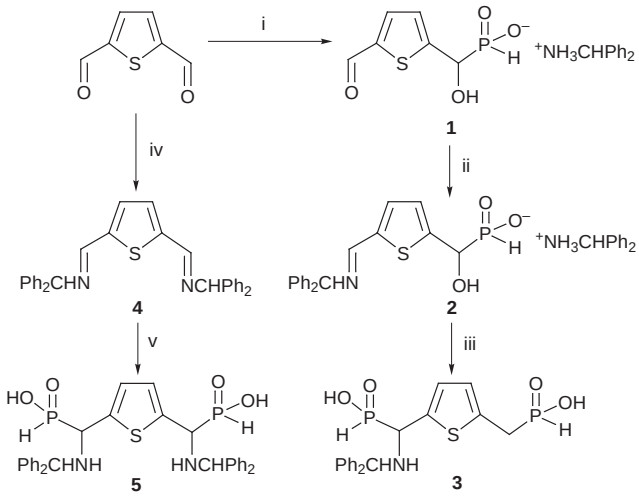
Reaction of 2,5-diformylthiophene with Ph_2CHNH_2 and hypophosphorus acid yields novel α-hydroxy- or α-aminomethylphosphinic acid derivatives depending on reaction conditions; the X-ray structure analysis of diphenylmethylammonium 5-formyl-2-thienyl(hydroxy)methylphosphinate provides the first direct structural information on the α-hydroxyalkylphosphinate class of compounds.

Compounds containing an α-aminoalkylphosphinic acid functional group are of considerable importance because of their anti-bacterial,[1] herbicidal[2] and fungicidal[3] activities. Protonation studies of α-aminomethylphosphinic acids [$R_2NCH_2P(H)O_2H$] have shown that the nitrogen atom is very weakly basic compared to those of α-aminomethylphosphonic acids ($R_2NCH_2PO_3H_2$) and α-aminocarboxylic acids ($R_2NCH_2CO_2H$), and that the phosphinic acid group is strongly acidic.[4] In contrast to the widely studied α-aminoalkylphosphinic acid derivatives, relatively few papers have been reported on the chemistry of α-hydroxyalkylphosphinic acids, although there is evidence that α-hydroxyalkylphosphinate esters are pharmaceutically active.[5] Many effective methods for the preparation of α-aminoalkylphosphinic acids have been developed,[6] but few synthetic routes to α-hydroxyalkylphosphinic acids have been reported and these involve prolonged heating of hypophosphorous acids with aldehydes or ketones,[7] or reaction of ketones with bis(trimethylsilyloxy)phosphine.[8] Here we have successfully prepared both types of α-functionalised phosphinates (Scheme 1); of particular importance is the isolation for the first time of the α-hydroxyalkylphosphinate compound using relatively mild reaction conditions, and the first characterisation by X-ray crystallography of this class of compound.



Scheme 1 *Reagents and conditions*: i, Ph_2CHNH_2, 50% aq H_3PO_2, 30%; ii, Ph_2CHNH_2, DMSO, 88%; iii, H_3PO_2, 1,4-dioxane, 26%; iv, Ph_2CHNH_2, MeOH, 51%; v, H_3PO_2, 1,4-dioxane, 72%

The reaction of 2,5-diformylthiophene (prepared as described in ref. 9) with Ph_2CHNH_2 and aqueous hypophosphorous acid (50%) gives an unexpected mono(α-hydroxyalkylphosphinate) derivative **1** rather than the bis(α-aminoalkylphosphinate) derivative **5**. The remaining thiophene carbonyl group is not electrophilic towards the addition of a second water molecule to form the intermediate *gem*-diol; all attempts to prepare the bis(α-hydroxyalkylphosphinate) derivative proved unsuccessful.

The presence of the α-hydroxy group in **1** was confirmed by X-ray structure analysis‡ of the (diphenylmethyl)ammonium salt and the structure of the ions, linked by a hydrogen bond between one of the phosphinate oxygen atoms and a proton of the ammonium cation [O(2)···H(1N) = 1.86 Å] is shown in Fig. 1(*a*). The remaining two protons of the (diphenylmethyl)-ammonium counterion are also involved in hydrogen-bonding to phosphinate oxygen atoms of adjacent symmetry related anions [O···H(N) = 1.72–1.90 Å], resulting in a complicated spiral hydrogen bonded chain of alternating cations and anions running parallel to the *b* axis of the crystal [Fig. 1(*b*)]. Along this helix, adjacent anions (separated by the *b* axis length) are linked by hydrogen-bonding between the α-hydroxy group of one and a phosphinate oxygen of the next [H(1O)···O(3) = 1.98 Å] as can also be seen in Fig. 1(*b*).

In order to prepare the bis(α-aminoalkylphosphinate) derivative **5** from the dialdehyde a two stage process was required. The carbonyl groups were first converted to the imine functions by condensing the dialdehyde and Ph_2CHNH_2 in MeOH to give **4**, and addition of hypophosphorous acid (100%) to **4** in 1,4-dioxane gives a diastereoisomeric mixture of **5** in good yield. However, the addition of hypophosphorous acid (100%) to the mono-imine derivative **2** readily converts the imine to the α-aminoalkylphosphinate, and the presence of excess hypophosphorous acid reduces the α-hydroxy functional group to yield **3**. Attempts to remove the Ph_2CH protecting groups have proved difficult. The new compounds **1–5** give satisfactory elemental analysis and their ^1H, ^{13}C and ^{31}P NMR data§ agree with the structures proposed. Both compounds **1** and **2** have been tested in the antibacterial screen and showed no activity.

Compound **1** is the first example of an α-hydroxyalkylphosphinate as a substituent of a heterocyclic ring. The ability to derivatize only one of the two aldehyde groups to afford the mono(α-hydroxyalkylphosphinate) opens up the possibility that the remaining carbonyl can be used in further reaction with an amine [*e.g.* Scheme 1(ii)]. This availability of an additional active carbonyl in an α-hydroxyalkylphosphinate derivative is thus potentially beneficial for its coupling to biological macromolecules or to polymers for selective metal complexation applications.

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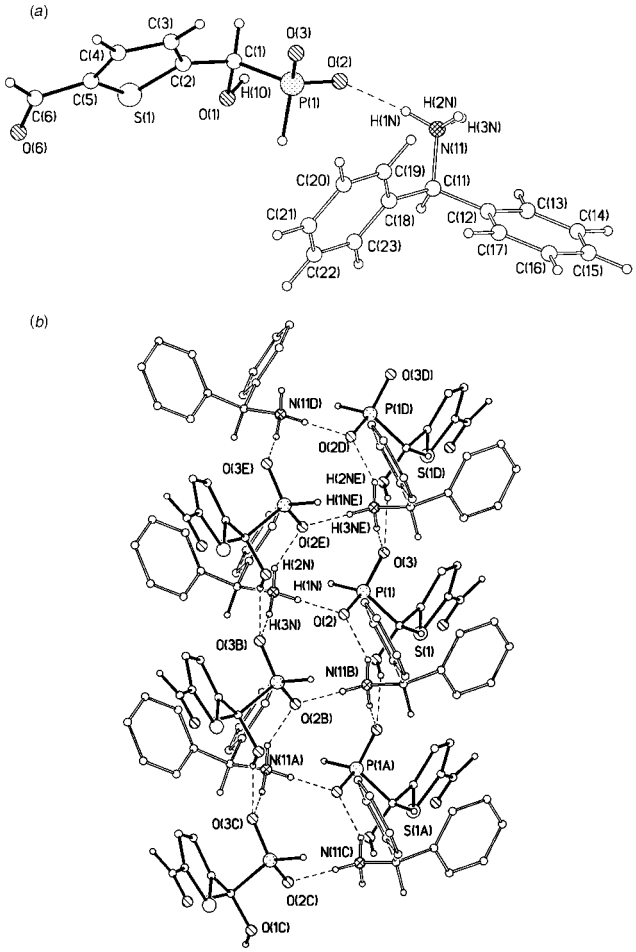

Fig. 1 The structure of **1**: (*a*) the anion and cation linked by one of the H-bonds (only the major component of the rotationally disorder formyl group is shown); (*b*) part of the helical H-bonded chain generated by the 2_1 screw axis parallel to *b* (the symmetry related ions are at A: *x*, −1 + *y*, *z*; B: 0.5 − *x*, −0.5 + *y*, 0.5 − *z*; C: 0.5 − *x*, −1.5 + *y*, 0.5 − *z*; D: *x*, 1 + *y*, *z*; E: 0.5 − *x*, 0.5 + *y*, 0.5 − *z*)

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Notes and References

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‡ *Crystal data* for **1**: $C_{19}H_{20}NO_4PS$, M = 389.2, pale brown crystal (0.50 × 0.38 × 0.34 mm³), monoclinic, space group $P2_1/n$ (No. 14), a = 15.773(3), b = 5.894(2), c = 21.404(4) Å, β = 104.06(4)°, U = 1930.2 Å³, Z = 4, $F(000)$ = 776, D_c = 1.278 g cm^{-3}, μ(Mo-Kα) = 0.26 mm^{-1}, λ = 0.71069 Å (graphite monochromator). Data were collected on a Philips PW1100 diffractometer in the θ range 3–23° with a scan width of 0.90°. The structure was solved by direct methods (ref. 10); the H-atoms of the ammonium and hydroxy group were located from difference-Fourier syntheses, but were not refined, and the remaining H-atoms were included at idealised positions. Anisotropic displacement parameters were assigned to all non-hydrogen atoms (apart from the phenyl C-atoms, which were constrained to idealised hexagons, C–C 1.395 Å) in the final cycles of full-matrix refinement based on F (ref. 11) which converged at R = 0.0561 (R_w = 0.0581, $w = 1/\sigma^2F_o$) for 1259 unique reflections having $I/\sigma(I) \geqslant 3.0$ and 174 variables. CCDC 182/972.

§ *Selected data* for **1**: δ_H(250 MHz, [$^2H_6$]DMSO) 9.81 (s, 1H, CHO), 9.37 (s, NH), 7.64 (m, 1H, thiophene), 7.35 (m, 10H, Ph), 7.10, (m, 1H, thiophene), 6.77 (d, 1H, J_{PH} 552, PH), 5.51 (s, 1H, $CHPh_2$), 4.70 (d, 1H, $^2J_{P–CH}$ 10.0, CH); δ_P 19.35; δ_C 183.6 (HCO), 147.2, 137.2, 132.4, 124.5, 134.6 (thiophene), 138.2, 128.6, 128.1, 127.1 (Ph), 69.1 (d, J_{PC} 107, CP), 56.9 ($CHPh_2$). For **2**: δ_H(250 MHz, [$^2H_6$]DMSO) 8.87 (s, NH), 8.55 (s, 1H, HCN), 7.25 (m, 21H, Ph and thiophene), 6.90 (m, 1H, thiophene), 6.64 (d, 1H, J_{PH} 489, PH), 5.62, 5.47 (s, 2H, $CHPh_2$), 4.49 (d, 1H, $^2J_{P–CH}$ 11.8, CH); δ_P 20.49; δ_C 1854.8 (HCN), 150.0, 139.5, 131.4, 123.4 (thiophene), 144.2, 139.2, 128.5, 128.1, 127.8, 127.1, 126.6 (Ph), 71.2 (d, J_{PC} 149, CP), 75.7, 56.9 ($CHPh_2$). For **3**: δ_H(250 MHz, [$^2H_6$]DMSO) 7.46–7.19 (m, 11H, Ph and thiophene), 6.84 (s, 1H, thiophene), 6.91 (d, 2H, J_{PH} 530, PH), 6.82 (d, 2H, J_{PH} 510, PH), 5.05 (s, 1H, $CHPh_2$), 3.78 (d, 1H, $^2J_{P–CH}$ 16.5, CH), 3.26 (d, 1H, $^2J_{P–CH}$ 17.5, CH_2); δ_P 27.76, 27.00; δ_C 146.6, 145.5, 141.5, 137.0,132.5, 131.3, 131.1, 130.7 (thiophene and Ph), 67.4 ($CHPh_2$), 60.1 (d, J_{PC} 101, HCP), 36.2 (d, J_{PC} 88.2, H_2CP). For **4**: δ_H(250 MHz, [$^2H_6$]DMSO) 8.66 (s, 2H, HCN), 7.52 (s, 2H, thiophene), 7.41–7.19 (m, 20H, Ph), 5.70 (s, 2H, $CHPh_2$); δ_C 154.9 (HCN), 144.5, 132.1 (thiophene), 143.9, 128.4, 127.1, 126.8 (Ph), 75.8 ($CHPh_2$). For **5**: diastereoisomers (*) δ_H(250 MHz, [$^2H_6$]DMSO) 7.35 (m, 21H, Ph and thiophene), 6.95, 6.88* (s, 1H, thiophene), 6.92 (d, 1H, J_{PH} 546, PH), 5.07, 5.04* (s, 1H, $CHPh_2$), 3.89, 3.83* (d, 1H, $^2J_{P–CH}$ 17.0, CH); δ_P; 27.26, 27.01*; δ_C 146.6, 146.3*, 145.3, 145.1*, 142.6, 142.0, 132.7, 132.5, 132.2, 131.4, 131.0 (Ph and thiophene), 67.5, 67.4* ($CHPh_2$), 60.3, 60.1* (d, J_{PC} 101, CP).

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